REMARKS

Upon entry of this amendment, claims 77-80 and 89-136 will be pending in the present application. Claims 77-80, 89-100, 109-116, and 125-136 are amended to limit the scope of the claims to gene-targeted mice. Claims 77-80 are amended to recite P264L as the mutation of the PS-1 gene. Claims 125, 127, 128, 130, 131, 133, 134, and 136 are amended to correct their dependencies in view of cancellation of claims. Claims 1-76, 81-88, and 137-140 are canceled. No new matter is introduced.

As an initial matter, Applicants note with appreciation consideration of the references submitted by way of information disclosure statements. As the information disclosure statements submitted to date comply with the requirements of 37 C.F.R. §§ 1.97 and 1.98, no further information regarding the cited references is required.

Claims 77-140 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Without conceding the correctness of the rejection, and to advance prosecution, Applicants have limited the claims to gene-targeted mice homozygous or heterozygous for a human mutation of the presenilin-1 (PS-1) gene wherein the mutation of the PS-1 gene is P264L and heterozygous or homozygous for an amyloid precursor protein (APP) gene having a human FAD Swedish mutation and a humanized Aβ nucleotide sequence. To the extent the rejection is applied to the amended claims, Applicants traverse.

The enablement requirement is fulfilled if any mode of making and using the invention is described. *Engel Industr. v. Lochformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991) ("[t]he enablement requirement is met if the description enables **any** mode of making and using the invention")(emphasis added); see also *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1071 (Fed. Cir. 2005) ("Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain.").

The inquiry is not whether experimentation is required, but rather whether the experimentation required is undue. According to the Federal Circuit, "a considerable amount

of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988) (citations omitted). For purposes of fulfilling the enablement requirement, it is sufficient that the specification describes the novel aspects of the invention, or provides specific starting materials or the conditions under which a process can be carried out. *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The "specification need not disclose what is well known in the art." *Id.*

The claims as amended herein are directed to gene-targeted mice homozygous or heterozygous for a human mutation of the presenilin-1 (PS-1) gene wherein the mutation of the PS-1 gene is P264L and heterozygous or homozygous for an amyloid precursor protein (APP) gene having a human FAD Swedish mutation and a humanized Aβ nucleotide sequence and their methods of use in identifying compounds having the ability to decrease *in vivo* levels of Aβ peptide or to treat Alzheimer's disease. The specification provides ample guidance regarding methods of making and using the claimed mice. Example 5 on pages 31-32 of the specification teaches methods of making PS-$1^{nP264L/+}$ x $APP^{NLh/+}$, PS-$1^{nP264L/nP264L}$ x $APP^{NLh/+}$, PS-$1^{nP264L/-}$ x $APP^{NLh/NLh}$, and PS-$1^{nP264L/nP264L}$ x $APP^{NLh/NLh}$ mice. Example 8 teaches methods for assessing the Aβ40 and Aβ42 levels in PS-$1^{nP264L/+}$ x $APP^{NLh/NLh}$ and PS-$1^{nP264L/nP264L}$ x $APP^{NLh/NLh}$ mice, the results of which are set forth in Table 2. Methods of making mice having an amyloid precursor protein (APP) gene having a human FAD Swedish mutation and a humanized Aβ nucleotide sequence were known in the art as exemplified by U.S. Patent No. 5,777,194 cited by Applicants on page 5 of the specification. A person of skill in the art would have been able to test various compounds according to the claimed methods in view of the guidance provided in the specification and knowledge and skill level in the art. In view of the breadth of the claims, the guidance and working examples provided by the Applicants, and the level of skill and knowledge in the art, Applicants respectfully request withdrawal of the enablement rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office action of record. An early and favorable action is therefore respectfully requested.

Respectfully submitted,

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